BEST AVAILABLE IMAGES

Defective images within this document are accurate representation of The original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 417/12, 277/54, A61K 31/425, 31/47 | A2

(11) International Publication Number: WO 96/30370

(43) International Publication Date: 3 October 1996 (03.10.96)

(21) International Application Number: PCT/JP96/00773

(22) International Filing Date: 26 March 1996 (26.03.96)

(30) Priority Data:

9506189.1	27 March 1995 (27.03.95)	GB
9511226.4	2 June 1995 (02.06.95)	GB

(81) Designated States: AU, CA, CN, HU, JP, KR, NO, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

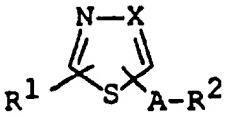
Published
Without international search report and to be republished upon receipt of that report.

(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

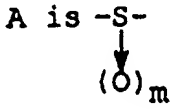
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MATSUO, Masaaki [JP/JP]; 4-12, Nakasakurazuka 5-chome, Toyonaka-shi, Osaka 560 (JP). OGINO, Takashi [JP/JP]; 41-34, Hiedacho, Yamatokooriyama-shi, Nara 639-11 (JP). TSUJI, Kiyoshi [JP/JP]; 170, Hatacho, Kishiwada-shi, Osaka 596 (JP).

(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaki-shi, Osaka 532 (JP).

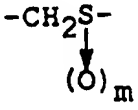
(54) Title: THIAZOLE AND THIADIAZOLE DERIVATIVES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS USEFUL IN THE TREATMENT OF THROMBOCYTOPENIA



(I)



(II)



(III)

(57) Abstract

A compound of formula (I) wherein R^1 is hydrogen, etc., R^2 is N- or S-containing unsaturated heterocyclic group, each of which may have suitable substituent(s), X is CH or N and A is (II) or (III) (wherein m is an integer of 0, 1 or 2) and a pharmaceutically acceptable salt thereof, which is useful as a medicament.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia
AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

DESCRIPTION

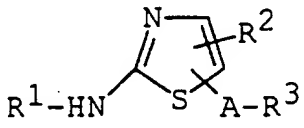
THIAZOLE AND THIADIAZOLE DERIVATIVES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS USEFUL IN THE TREATMENT OF THROMBOCYTOPENIA

TECHNICAL FIELD

This invention relates to new heterocyclic compounds and pharmaceutically acceptable salts thereof which are useful as a medicament.

PRIOR ART

EP-A-0412404 discloses the thiazole derivatives of the following formula and also discloses that they are useful for the treatment and prophylaxis of thrombocytopenia, etc.



wherein

R^1 is hydrogen or acyl,

R^2 is hydrogen, etc.,

A is $-S(O)_m-$ or $-CH_2S(O)_m-$ [wherein m is 0, 1 or 2], etc., and

R^3 is N-containing unsaturated heterocyclic group, etc.

DISCLOSURE OF INVENTION

This invention relates to new heterocyclic compounds and pharmaceutically acceptable salts thereof which have pharmacological activities, processes for production thereof, pharmaceutical compositions comprising the same and methods

of use thereof.

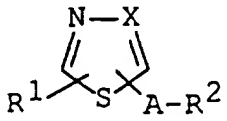
Accordingly, one object of this invention is to provide new and useful heterocyclic compounds and pharmaceutically acceptable salt thereof.

Another object of this invention is to provide processes for production of said heterocyclic compounds and pharmaceutically acceptable salts thereof.

A further object of this invention is to provide pharmaceutical compositions comprising said heterocyclic compounds of pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide methods of using said heterocyclic compounds or pharmaceutically acceptable salts thereof for the prophylactic or therapeutic treatment of thrombocytopenia [e.g. idiopathic thrombocytopenic purpura, secondary thrombocytopenic purpura, thrombocytopenia due to a side effect of an antitumor agent (e.g. mitomycin C, etc.) etc.], nephritis, rheumatism (e.g. rheumarthritis, etc.), tumor, side effect of an antitumor agent (e.g. decrease of body weight, etc.), and the like in human being and animals.

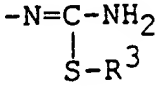
The object heterocyclic compounds of this invention are novel and represented by the following general formula (I) :



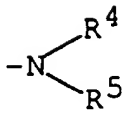
(I)

wherein

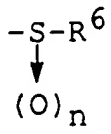
R^1 is hydrogen, halogen, amino, acylamino, thioureido, guanidino,



(wherein R^3 is lower alkyl),



(wherein R^4 is acylamino or lower alkyl which may have suitable substituent(s) and
R^5 is hydrogen or acyl),

or 

(wherein R^6 is N-containing unsaturated heterocyclic group and
n is an integer of 0, 1 or 2),

R^2 is N- or S-containing unsaturated heterocyclic group, each of which may have suitable substituent(s),

X is CH or N and

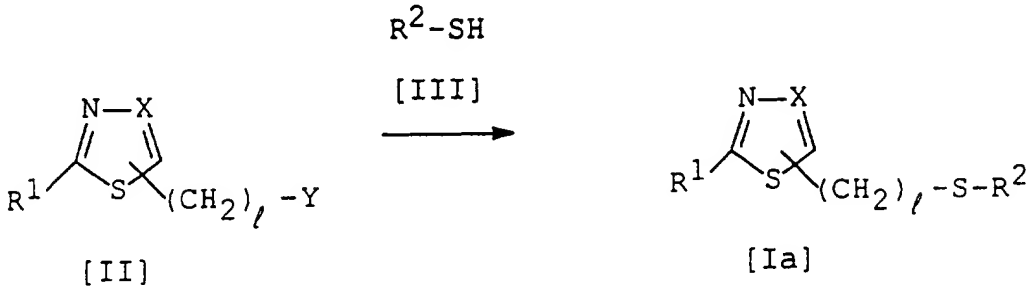
A is  (wherein m is an integer of 0, 1 or 2),

provided that R^2 is quinolyl, quinoxalinyl, quinazolinyl, naphthyridinyl, benzimidazolyl, purinyl, thienyl, thiazolyl, thiazolinyl, triazolyl, pyridyl N-oxide or 1,2,3-thiadiazolyl, each of which may be substituted with lower alkyl, lower alkylthio, halogen, nitro, amino, acyl or acylamino,

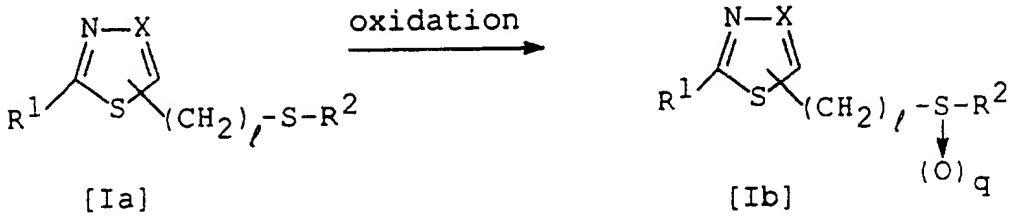
when X is CH and R^1 is amino or acylamino.

The object compound (I) of the present invention can be prepared by the following processes.

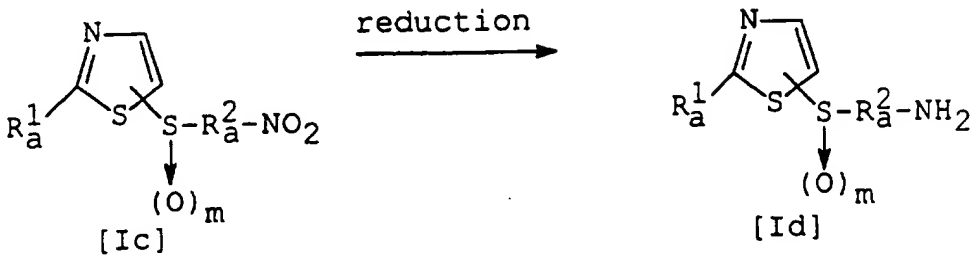
Process 1



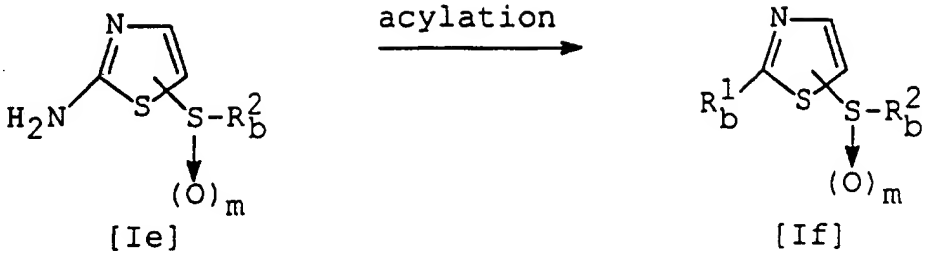
Process 2



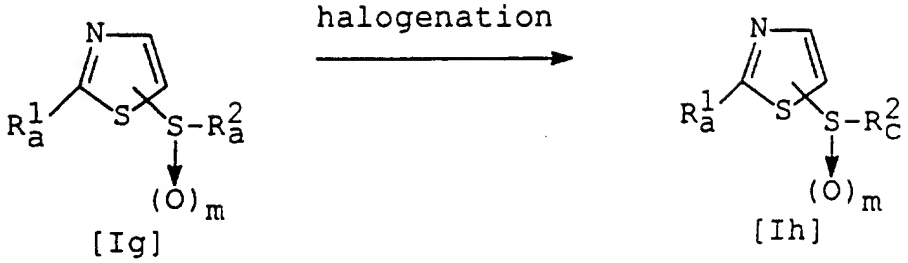
Process 3



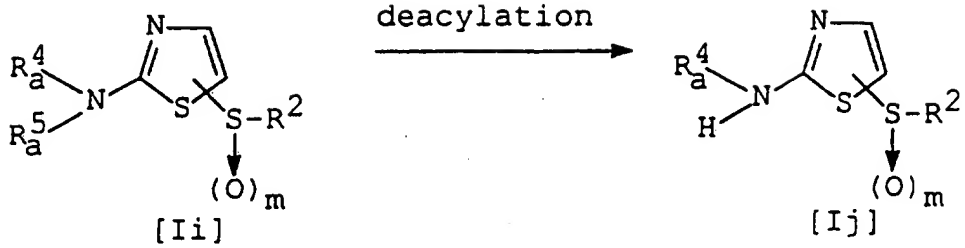
Process 4



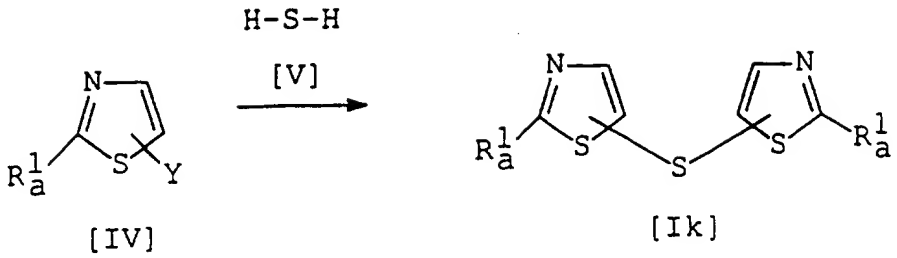
Process 5



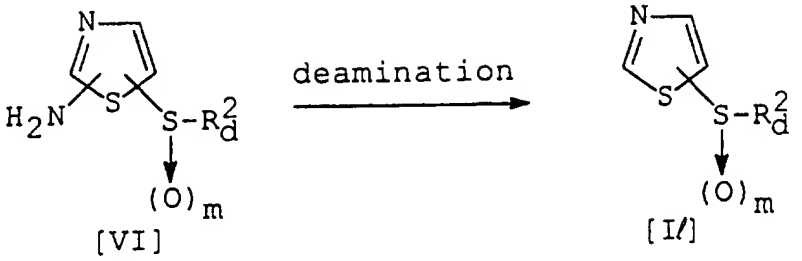
Process 6



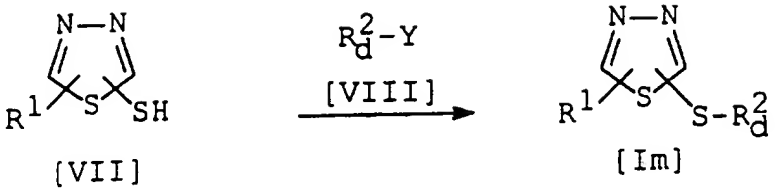
Process 7



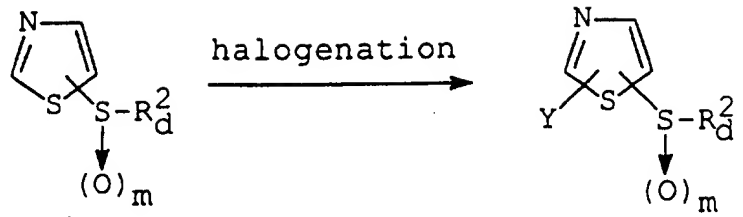
Process 8



Process 9

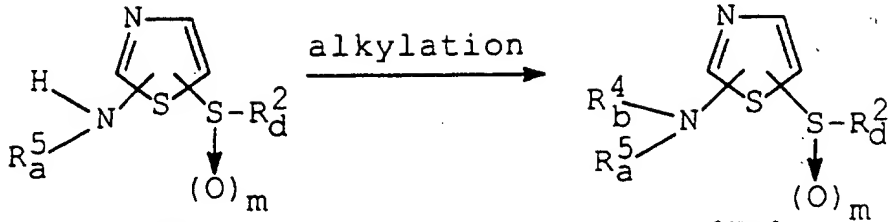


Process 10



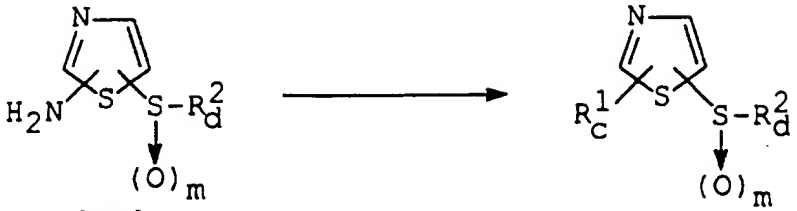
[Il] [In]

Process 11



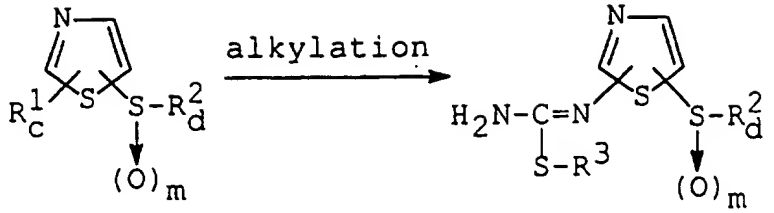
[IX] [Ir]

Process 12



[VI] [Io]

Process 13



Process 14

wherein

R^1, R^2, R^3, X and m are each as defined above,

R^1_a is amino or acylamino,

R^1_b is acylamino,

R^1_c is thioureido,

R^1_d is guanidino,

R^2_a is quinolyl, quinoxalinyl, quinazolinyl, naphthyridinyl, benzimidazolyl, purinyl, thienyl, thiazolyl,

thiazolinyl, triazolyl, pyridyl N-oxide or 1,2,3-thiadiazolyl,

R^2_b is quinolyl, quinoxalinyl, quinazolinyl, naphthyridinyl, benzimidazolyl, purinyl, thienyl, thiazolyl, thiazolinyl, triazolyl, pyridyl N-oxide or 1,2,3-thiadiazolyl, each of which may be substituted with lower alkyl, lower alkylthio, halogen, nitro, amino, acyl or acylamino,

R^2_c is quinolyl, quinoxalinyl, quinazolinyl, naphthyridinyl, benzimidazolyl, purinyl, thienyl, thiazolyl, thiazolinyl, triazolyl, pyridyl N-oxide or 1,2,3-thiadiazolyl, each of which has halogen,

R^2_d is N-containing unsaturated heterocyclic group,

R^4_a is hydrogen or lower alkyl which may have suitable substituents,

R^4_b is lower alkyl which may have suitable substituents,

R^5_a is acyl,

Y is halogen,

ℓ is an integer of 0 or 1, and

q is an integer of 1 or 2.

In the above and subsequent description of the present specification, suitable examples and illustrations for the various definitions to be included within the scope of the invention are explained in detail as follows :

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

Suitable "lower alkyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl or the like, in which preferable one is C_1-C_4 lower alkyl such as methyl, ethyl, propyl, isobutyl or tert-butyl.

Suitable example of "lower alkyl" moiety in the term "lower alkylthio" can be referred to the ones as exemplified

above.

Suitable "halogen" may include fluorine, chlorine, bromine and iodine.

Suitable "acyl" may include an aliphatic acyl, an aromatic acyl and an aliphatic acyl substituted with aromatic group(s).

The aliphatic acyl may include saturated or unsaturated, acyclic or cyclic ones, such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, etc.), lower alkanesulfonyl [e.g. methanesulfonyl, ethanesulfonyl, propanesulfonyl, butanesulfonyl, pentanesulfonyl, hexanesulfonyl, etc.], lower alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl, etc.), carbamoyl and the like.

The aromatic acyl may include aroyl (e.g. benzoyl, toluoyl, xyloyl, etc.) and the like.

The aliphatic acyl substituted with aromatic group(s) may include ar(lower)alkanoyl such as phenyl(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, phenylhexanoyl, etc.), ar(lower)alkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), phenoxy(lower)alkanoyl (e.g. phenoxyacetyl, phenoxypropionyl, etc.), and the like.

Among them, preferable acyl is lower alkanoyl such as formyl, acetyl, propionyl, etc.

Suitable example of "acyl" moiety in the term of "acylamino" can be referred to the ones as exemplified above.

Preferable acylamino for R^1 and R^4 is lower alkanoylamino such as formylamino, acetylamino, etc.

Suitable substituent(s) in lower alkyl for R^4, R^4_a and R^4_b may include 2-oxo-1,3-dioxolyl which may have lower alkyl, etc.

Suitable "N-containing unsaturated heterocyclic group"

for R^2, R^2_a and R^6 may be one containing at least one nitrogen atom and may include monocyclic or polycyclic heterocyclic group, and preferable heterocyclic group may be unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;
unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), quinoxalinyl, naphthyridinyl, purinyl, quinazolinyl, etc.;
unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., benzoxazolyl, benzoxadiazolyl, etc.);
unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl, etc.), thiazolinyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like.

Suitable S-containing unsaturated heterocyclic group may include thienyl, thianthrenyl, and the like.

Said "N- and S-containing unsaturated heterocyclic group" may have 1 to 4 substituents, and suitable substituent

is lower alkyl, lower alkylthio, halogen, nitro, amino, acyl, acylamino, as exemplified above, and the like.

Among them, preferable "N-containing unsaturated heterocyclic group" is

(1) unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms, more preferably pyridyl,

(2) unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, more preferably quinolyl, or

(3) unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, more preferably thiazolyl.

Preferable "N-containing unsaturated heterocyclic group" for R^6 is pyridyl.

Suitable pharmaceutically acceptable salts of the object compounds [I] are conventional non-toxic salts and include an organic acid salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic acid salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], a salt with an amino acid [e.g. arginine, glutamic acid, ornithine, etc.], a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.], and the like.

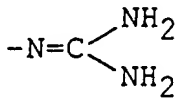
The object compounds (I) and a pharmaceutically acceptable salt thereof may include a solvate [e.g., enclosure compound (e.g., hydrate, etc.)].

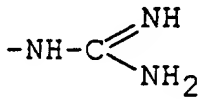
In this respect, it is to be noted that the compounds [Ia] to [Ir] are included within the scope of the compound

[I], and accordingly the suitable salts and a solvate of these compounds [Ia] to [Ir] are to be referred to those as exemplified for the object compounds [I] in the above.

Further, it is to be noted that the object compound (I) may include one or more stereoisomer(s) due to asymmetric carbon atom(s) and double bond(s) and all such isomers and mixture thereof are included within the scope of this invention.

Regarding the object compound (I), it is to be understood that they include tautomeric isomers.

That is, a group of the formula : 

can be also alternatively represented by its tautomeric formula : 

The processes for preparing the object compound [I] or salts thereof are explained in detail in the following.

Process 1

The object compound [Ia] or its salt can be prepared by reacting a compound [II] or its salt with a compound [III] or its salt.

Suitable salts of the compound [II] and [III] may be the same as those exemplified as base salts of the object compound [I].

This reaction is usually carried out in a solvent such as methanol, ethanol, propanol, tetrahydrofuran, dioxane,

dimethylformamide or any other organic solvent which does not adversely influence the reaction.

In case that a free form of the compound [III] is used in this reaction, the reaction is preferably carried out in the presence of a conventional base, such as alkali metal hydride [e.g. sodium hydride, potassium hydride, etc.], alkaline earth metal hydride [e.g. calcium hydride, magnesium hydride, etc.], alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], alkali metal fluoride [e.g. potassium fluoride, cesium fluoride, etc.], alkali metal alkoxide [e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.], trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4,3,0]non-5-ene, 1,4-diazabicyclo[2,2,2]octane, 1,5-diazabicyclo[5,4,0]-undecene-5 or the like.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under cooling, warming or heating.

Process 2

A compound [Ib] or its salt can be prepared by subjecting a compound [Ia] or its salt to oxidation.

Oxidation in this process is carried out in a conventional manner with a conventional oxidizing agent which can oxidize a -S- group into -SO- or $-SO_2-$ group.

Suitable example of such oxidizing agent are inorganic peracid or its salt (e.g. periodic acid, persulfuric acid, etc.) or the sodium or potassium salt thereof, an organic peracid or its salt (e.g. perbenzoic acid, 3-chloroperbenzoic acid, performic acid, peracetic acid, chloroperacetic acid, trifluoroperacetic acid, etc. or the sodium or potassium salt thereof, etc.), ozone, hydrogen peroxide, urea-hydrogen

peroxide and the like.

The present reaction is preferably conducted in the presence of a compound comprising a Group Vb or VIb metal in the Periodic Table, for example, tungstic acid, molybdic acid, vanadic acid, etc. or their salt with an alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. calcium, magnesium, etc.) or ammonium, etc., or vanadium pentoxide.

The present oxidation is usually conducted in a solvent such as water, acetic acid, ethyl acetate, chloroform, dichloromethane, tetrahydrofuran, dioxane, N,N-dimethylformamide or any other solvent which does not give bad influence to the present reaction.

There is not particular limitation to the reaction temperature, and the present reaction is usually conducted at ambient temperature or under cooling.

Process 3

The object compound [Id] or its salt can be prepared by reducing a compound [Ic] or its salt.

The reduction can be carried out in a conventional manner, namely, chemical reduction or catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal (e.g. stannum, zinc, iron, etc.) and ammonium chloride or an base (e.g. ammonia, sodium hydroxide, etc.), a combination of metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, stannous chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.), alkali metal borohydride (e.g. lithium borohydride, sodium borohydride, potassium borohydride, etc.) alkali metal cyanoborohydride (e.g. sodium cyanoborohydride, etc.) or alkali metal ammonium hydride (e.g. lithium aluminum hydride, etc.) or the like.

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalyst (e.g. palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalyst (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalyst (e.g. reduced cobalt, Raney cobalt, etc.), iron catalyst (e.g. reduced iron, Raney iron, etc.), copper catalyst (e.g. reduced copper, Raney copper, Ullman copper, etc.) or the like.

The reduction of this process is usually carried out in a solvent such as water, alcohol (e.g. methanol, ethanol, propanol, etc.), acetic acid, dioxane, tetrahydrofuran, N,N-dimethylformamide, dimethyl sulfoxide, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof. In case above-mentioned reducing agent is liquid, it can be also used as a solvent.

The reaction is preferably carried out under cooling to warming or heating.

Process 4

The object compound [If] or its salt can be prepared by acylating a compound [Ie] or its reactive derivatives at the amino group or a salt thereof.

Suitable reactive derivatives at the amino group of the compound [Ie] include conventional ones used in amidation for example, Schiff's base type imino or its tautomeric enamine type isomer formed by reaction of a compound [Ie] with a carbonyl compound, a silyl derivative formed by reaction of a compound [Ie] with a silyl compound such as trimethylsilylacetamide, bis(trimethylsilyl)acetamide or the like, a derivative formed by reaction of a compound [Ie] with phosphorus trichloride or phosgene, and the like.

Suitable acylating agent to be used in this reaction

includes an organic acid such as alkanoic acid [e.g. formic acid, acetic acid, propionic acid, etc.], arenecarboxylic acid (e.g. benzoic acid, toluenecarboxylic acid, etc.) which may have halogen, lower alkanesulfonic acid [e.g. methanesulfonic acid, etc.], arylisocyanate [e.g. phenylisocyanate, etc.] which may have halogen and their reactive derivative.

The suitable reactive derivative may be a conventional one such as an acid halide [e.g. acid chloride, acid bromide, etc.], an acid azide, an acid anhydride, an activated amide, an activated ester and the like. When free acid is used as an acylating agent, the acylation reaction may preferably be conducted in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide or the like.

This reaction is usually carried out in a solvent which does not adversely influence the reaction such as water, tetrahydrofuran, chloroform, dioxane, pyridine, methylene chloride, N,N-dimethylformamide or the like.

The reaction temperature is not critical and the reaction can be carried out at any temperature under cooling to heating.

In this process when the starting compound [Ie] or its salt has an amino group or imino group for R_b^2, the group is also converted to an acylamino group or acylimino group.

Process 5

The object compound [Ih] or its salt can be prepared by halogenating a compound [Ig] or its salt.

Suitable halogenating agent of this reaction may include conventional ones for example, halogen [e.g. chlorine, bromine, iodine, etc.], sulfuryl halide [e.g. sulfuryl chloride, sulfuryl bromide, etc.], N-halosuccinimide [e.g. N-chlorosuccinimide, N-bromosuccinimide, etc.], pyridinium hydrohalide perhalide [e.g. pyridinium hydrobromide

perbromide, pyridinium hydrochloride perchloride, etc.], quarternary ammonium perhalide [e.g. phenyltrimethylammonium perbromide, etc.], ω-trihaloacetophenone [e.g. ω-tribromoacetophenone, etc.], cupric or potassium bromide, selenium oxychloride, or the like. These halogenating agents may be selected according to the kind of the starting compound [Ig] to be used.

This reaction is usually carried out in a conventional solvent such as chloroform, methylene chloride, carbon tetrachloride, acetic acid, a mixture of hydrogen halide [e.g. hydrogen bromide, hydrogen chloride, etc.] and acetic acid, water, dimethylformamide or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming or heating.

Process 6

The object compound [Ij] or its salt can be prepared by deacylating a compound [Ii] or its salt.

Suitable method for this deacylation reaction may include conventional one such as hydrolysis and the like.

Hydrolysis is preferably carried out in the presence of an acid.

Suitable acid may be an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.], an organic acid [e.g. formic acid, acetic acid, trifluoroacetic acid, propionic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.], an acidic ion-exchange resin and the like. In case that the organic acid such as trifluoroacetic acid and p-toluenesulfonic acid is used in this reaction, the reaction is preferably carried out in the presence of cation trapping agents [e.g. anisole, etc.].

The acid suitable for this hydrolysis can be selected according to the kinds of the acyl group to be removed.

The hydrolysis is usually carried out in a conventional

solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, tert-butyl alcohol, tetrahydrofuran, N,N-dimethylformamide, dioxane or a mixture thereof, and further the above-mentioned acids can also be used as a solvent when they are in liquid.

The reaction temperature of this hydrolysis is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under heating.

In this process, when the starting compound [Ii] or its salt has an acylamino group for R^2, the group is also converted to an amino group.

Process 7

The object compound [Ik] or its salt can be prepared by reacting a compound [IV] or its salt with a compound [V] or its salt.

Suitable salts of the compound [IV] and [V] may be the same as those exemplified as base salts of the object compound [I].

This reaction is usually carried out in a solvent such as methanol, ethanol, propanol, tetrahydrofuran, dioxane, dimethylformamide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under cooling, warming or heating.

Process 8

The object compound [Iℓ] or its salt can be prepared by subjecting the compound [VI] or its reactive derivative at the amino group or a salt thereof to a deamination reaction.

Suitable reactive derivatives at the amino group of the compound [VI] include conventional ones for example, Schiff's base type imino or its tautomeric enamine type isomer formed by reaction of a compound [VI] with a carbonyl compound, a

silyl derivative formed by reaction of a compound [VI] with a silyl compound such as trimethylsilylacetamide, bis(trimethylsilyl)acetamide or the like, a derivative formed by reaction of a compound [VI] with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound [VI] may be the same as those as base salts of the object compound [I].

The deamination reaction is carried out in accordance with a conventional method such as reaction of the compound [VI] with a nitrous acid ester, or the like.

Suitable nitrous acid ester may be isoamyl nitrite, amyl nitrite or the like.

The reaction is usually carried out in a conventional solvent such as tetrahydrofuran, acetic acid, propionic acid, dioxane, ethanol, dimethylformamide, or the like.

The reaction temperature is not critical, and the reaction is preferably carried out at ambient temperature or under heating.

Process 9

The object compound [Im] or its salt can be prepared by reacting a compound [VII] or its salt with a compound [VIII] or its salt.

Suitable salts of the compound [VII] and [VIII] may be the same as those exemplified for the object compound [I].

This reaction may be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 10

The object compound [In] or its salt can be prepared by halogenating a compound [Iℓ] or its salt.

This reaction may be carried out in substantially the

same manner as Process 5, and therefore the reaction mode and reaction conditions [e.g. halogenating agent, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 5.

Process 11

The object compound [Ir] or its salt can be prepared by subjecting a compound [IX] or its salt to alkylation reaction.

The alkylating agent to be used in the present alkylation reaction may include di(lower)alkyl sulfate [e.g. dimethyl sulfate, diethyl sulfate, etc.], diazo(lower)alkane [e.g. diazomethane, diazoethane, etc.], lower alkyl halide [e.g. methyl iodide, ethyl iodide, etc.], lower alkyl sulfonate [e.g. methyl p-toluene-sulfonate, etc.], and the like.

The reaction using di(lower)alkyl sulfate, lower alkyl halide or lower alkyl sulfonate is usually carried out in a solvent such as water, acetone, ethanol, ether tetrahydrofuran dimethylformamide or any other solvent which dose not adversely influence the reaction. The present reaction is preferably carried out in the presence of a base such as an inorganic base or an organic base as mentioned for Process 1. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating around boiling point of the solvent.

The reaction using diazoalkane is usually carried out in a solvent such as ether, tetrahydrofuran or the like. The reaction temperature is not critical and the reaction is usually carried out under cooling or at ambient temperature.

Process 12

The object compound [Io] or its salt can be prepared by reacting the compound [VI] or its reactive derivative at the amino group or a salt thereof with an alkali metal isocyanate

(e.g. sodium isocyanate, potassium isocyanate, etc.).

This reaction is usually carried out in a conventional solvent such as water, methanol, ethanol, isopropyl alcohol, tetrahydrofuran, dioxane, chloroform, acetone, methylene chloride, dimethylacetamide, dimethylformamide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under warming or heating.

Process 13

The object compound [Ip] or its salt can be prepared by subjecting a compound [Io] or its salt to alkylation reaction.

This reaction may be carried out in substantially the same manner as Process 11, and therefore the alkylating agent, the reaction mode and reaction conditions [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 11.

Process 14

The object compound [Iq] or its salt can be prepared by reacting a compound [Ip] or its salt in a presence of ammonia.

This reaction is usually carried out in a conventional solvent such as water, alcohol (e.g. methanol, ethanol, propanol, etc.), tetahydrofuran, dioxane, ethyl acetate, N,N-dimethylformamide, or the like.

The reaction temperature is not critical, and the reaction preferably carried out under heating.

The object compounds [I] and pharmaceutically acceptable salts thereof are novel and exhibit pharmacological activities and are useful for the treatment and prophylaxis of thrombocytopenia [e.g. idiopathic thrombocytopenic

purpura, secondary thrombocytopenic purpura, thrombocytopenia due to a side effect of an antitumor agent (e.g. mitomycin C, etc.) etc.], nephritis, rheumatism (e.g. rheumarthritis, etc.), tumor, side effect of an antitumor agent (e.g. decrease of body weight, etc.) and the like.

In order to show the utility of the object compounds [I], platelet number-increasing activities of the object compound [I] is explained in the following.

Platelet number-increasing activity

Test Increasing effect on the platelet number decreased by mitomycin C

Method :

A test compound (100 mg/kg) was given orally once a day for 5 days to male ddY mice aged 6 or 7 weeks.

The animals were used in groups of 10. Mitomycin C (hereinafter referred to as MMC) at a dose of 3.2 mg/kg was given intravenously to mice on day 0, 2 and 4 after the initial dosing with the test compound. The number of platelets were counted 5 days after the final dosing with the test compound, in which mice were bled from the orbital plexus and the platelets were counted with an automatic blood analyzer. The number of platelets of each group was calculated on the basis of the number of platelets (%) obtained from the normal control group (no test compound and no MMC group).

Results :

Test Compound	Platelet (% of normal control)
Example 1	74**
Example 2-12	58*
Example 3	79*
Example 4-1	71*
Example 4-5	62**
Example 4-6	54*
Example 6-4	66*
Example 11-5	72*
Example 20-1	91*
MMC control	42

Student t-test : * $P<0.05$, ** $P<0.01$ vs MMC control (no test compound)

For therapeutic administration, the object compounds [I] and pharmaceutically acceptable salts thereof are used in the form of conventional pharmaceutical composition such as powders, fine granules, granules, tablets, dragee, microcapsules, capsules, suppository, solution, suspension, emulsion, syrups and the like. If desired, diluents or disintegrators (e.g. sucrose, lactose, starch, crystalline cellulose, low-substituted hydroxypropyl cellulose, synthetic aluminum silicate, etc.), binding agents (e.g. cellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polypropylpyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, etc.), coloring agents, sweeting agents, lubricant (e.g. magnesium stearate, etc.) or the like, may be dispensed with said composition.

The dosage of said composition according to this invention depends on the patient's age, body weight,

condition, etc., and it is generally administered by the oral route at the daily dose level of 1 mg to 1 g as the object compound [I] or a salt thereof, preferably 10 mg to 100 mg on the same basis, at the interval of 1 to 3 times a day. Typical unit doses may be 5 mg, 10 mg, 20 mg, 50 mg, 100 mg and the like, although these are only examples and not limitative, of course.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

A mixture of acetic anhydride (5.5 g) and formic acid (2.5 g) was stirred at 50°C for 30 minutes. To the mixture was added 2-amino-5-(2-pyridylsulfinyl)thiazole (4 g) at room temperature. The resulting mixture was stirred for 2 hours, poured into ice-water, neutralized with sodium bicarbonate, and extracted with a mixture of tetrahydrofuran and ethyl acetate. The extract was washed with water, dried, and evaporated to dryness. The residue was recrystallized from a mixture of tetrahydrofuran and ethanol to give crystals of 2-formylamino-5-(5-pyridylsulfinyl)thiazole (4 g).

mp : 198-200°C (dec.)

IR (Nujol) : 3170, 3080, 1685, 1575 cm^{-1}

NMR (DMSO-d_6, δ) : 7.5-7.7 (1H, m), 8.0-8.3 (2H, m), 8.26 (1H, s), 8.54 (1H, s), 8.6-8.7 (1H, m)

MASS (m/z) : 254 (M+1)

Anal. Calcd. for $C_9H_7N_3O_2S_2$: C 42.68, H 2.77, N 16.60

Found : C 42.35, H 2.66, N 16.20

Preparation 2

A mixture of chloroacetaldehyde (40% in water; 25 ml), 1-acetyl-3-thiosemicarbazide (13 g) and sodium acetate (13 g) in ethanol (200 ml) was stirred under reflux for 4 hours.

The solvent was evaporated, and the residue was dissolved in a mixture of tetrahydrofuran and ethyl acetate and washed with water. The organic extract was dried and concentrated to dryness. The residue was purified by column chromatography on silica gel eluting with a mixture of chloroform and methanol (10:1) to give crystals of 2-(2-acetylhydrazino)thiazole (10.1 g).

mp : 145-147°C

IR (Nujol) : 3200, 1670, 1580, 1520, 1490 cm^{-1}

NMR (DMSO-d_6, δ) : 1.88 (3H, s), 6.78 (1H, d, J=4Hz), 7.11 (1H, d, J=4Hz), 9.24 (1H, s), 10.09 (1H, s)

MASS (m/z) : 158 (M+1)

Example 1

A mixture of 2-amino-5-chlorothiazole hydrochloride (1.36 g), 2-quinolinethiol (1.35 g) and sodium bicarbonate (2 g) in N,N-dimethylformamide (20 ml) was stirred under nitrogen at 110°C for 2 hours. The solvent was evaporated and the residue was dissolved in a mixture of tetrahydrofuran and ethyl acetate and washed with water. The organic extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue (2 g) was purified by column chromatography on silica gel eluting with a mixture of chloroform and methanol (10:1) to give a brown powder of 2-amino-5-(2-quinolylthio)thiazole (1.4 g).

mp : 168-170°C

IR (Nujol) : 3275, 3100, 1630, 1585, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 7.22 (1H, d, J=8Hz), 7.33 (1H, s), 7.5-8.0 (6H, m), 8.28 (1H, d, J=8Hz)

MASS (m/z) : 260 (M+1)

Anal. Calcd. for $C_{12}H_9N_3S_2$: C 55.60, H 3.47, N 16.22

Found : C 55.14, H 3.39, N 16.00

Example 2

The following compounds were obtained according to a

similar manner to that of Example 1.

(1) 2-Amino-5-(2-quinoxalinylthio)thiazole
mp : 160°C
IR (Nujol) : 3280, 3100, 1670, 1550, 1535, 1490 cm^{-1}
NMR (DMSO-d_6, δ) : 7.38 (1H, s), 7.65 (2H, broad s), 7.7-8.1 (4H, m), 8.68 (1H, s)
MASS (m/z) : 261 (M+1)
Anal. Calcd. for $C_{11}H_8N_4S_2$: C 50.77, H 3.08, N 21.54
Found : C 50.50, H 3.04, N 21.07

(2) 2-Amino-5-(1,8-naphthyridin-2-ylthio)thiazole
mp : 194-195°C
IR (Nujol) : 1595, 1510 cm^{-1}
NMR (DMSO-d_6, δ) : 7.34 (1H, s), 7.36 (1H, d, J=8Hz), 7.5-7.7 (3H, m), 8.3-8.5 (2H, m), 8.9-9.1 (1H, m)
MASS (m/z) : 261 (M+1)
Anal. Calcd. for $C_{11}H_8N_4S_2$: C 50.77, H 3.08, N 21.54
Found : C 51.32, H 3.07, N 21.00

(3) 2-Amino-5-[6-(methylthio)-2-quinolylthio]thiazole
mp : 137-138°C
IR (Nujol) : 3450, 1630, 1575, 1520 cm^{-1}
NMR (DMSO-d_6, δ) : 2.58 (3H, s), 7.19 (1H, d, J=8Hz), 7.32 (1H, s), 7.5-7.8 (5H, m), 8.19 (1H, d, J=8Hz)
MASS (m/z) : 306 (M+1)
Anal. Calcd. for $C_{13}H_{11}N_3S_3$: C 51.15, H 3.61, N 13.77
Found : C 51.24, H 3.64, N 13.46

(4) 2-Amino-5-(6-methyl-2-quinolylthio)thiazole
mp : 180-181°C
IR (Nujol) : 3400, 1600, 1585, 1510 cm^{-1}
NMR (DMSO-d_6, δ) : 2.47 (3H, s), 7.18 (1H, d, J=8Hz), 7.32 (1H, s), 7.5-7.8 (5H, m), 8.18 (1H, d, J=8Hz)
MASS (m/z) : 274 (M+1)

Anal. Calcd. for $C_{13}H_{11}N_3S_2$: C 57.14, H 4.03, N 15.38
Found : C 57.99, H 4.15, N 15.35

(5) 2-Amino-5-(6-fluoro-2-quinolylthio)thiazole
mp : 189-190°C
IR (Nujol) : 3400, 1600, 1590, 1560, 1510 cm^{-1}
NMR (DMSO-d_6, δ) : 7.28 (1H, d, J=8Hz), 7.34 (1H, s), 7.6-8.0 (5H, m), 8.28 (1H, d, J=8Hz)
MASS (m/z) : 278 (M+1)
Anal. Calcd. for $C_{12}H_8FN_3S_2$: C 51.99, H 2.89, N 15.16
Found : C 52.38, H 2.86, N 15.13

(6) 2-Amino-5-(8-quinolylthio)thiazole
mp : 243-246°C (dec.)
IR (Nujol) : 3300, 1635, 1520, 1490 cm^{-1}
NMR (DMSO-d_6, δ) : 7.21 (1H, dd, J=1, 7Hz), 7.29 (1H, s), 7.5-7.8 (5H, m), 8.31 (1H, dd, J=2, 8Hz), 8.9-9.0 (1H, m)
MASS (m/z) : 259 (M)

(7) 2-Amino-5-(2-benzimidazolylthio)thiazole
mp : 208-210°C (dec.)
IR (Nujol) : 3350, 3100, 1620, 1520 cm^{-1}
NMR (DMSO-d_6, δ) : 7.1-7.2 (2H, m), 7.34 (1H, s), 7.4-7.5 (2H, m), 7.56 (2H, s)
MASS (m/z) : 248 (M)

(8) 2-Amino-5-(5-nitro-2-benzimidazolylthio)thiazole
mp : 243-245°C (dec.)
IR (Nujol) : 3350, 1620, 1520 cm^{-1}
NMR (DMSO-d_6, δ) : 7.41 (1H, s), 7.60 (1H, d, J=9Hz), 7.68 (2H, s), 8.07 (1H, dd, J=2, 9Hz), 8.32 (1H, d, J=2Hz), 12.95 (1H, s)
MASS (m/z) : 293 (M)

(9) 2-Amino-5-(6-purinylthio)thiazole

mp : 208-210°C (dec.)

IR (Nujol) : 3300, 1600, 1570, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 7.23 (1H, s), 7.49 (2H, s), 8.51 (1H, s), 8.66 (1H, s)

MASS (m/z) : 250 (M), 208

Anal. Calcd. for $C_8H_6N_6S_2 \cdot 1/3H_2O$: C 37.50, H 2.50, N 32.81

Found : C 37.74, H 2.36, N 32.60

(10) 2-Amino-5-(2-thienylthio)thiazole

mp : 76-80°C

IR (Nujol) : 3400, 1600, 1510 cm^{-1}

NMR ($CDCl_3$, δ) : 5.34 (2H, s), 6.9-7.0 (1H, m), 7.1-7.2 (1H, m), 7.21 (1H, s), 7.2-7.4 (1H, m)

MASS (m/z) : 214 (M)

(11) 2-Amino-5-(2-thiazolylthio)thiazole

IR (Nujol) : 3300, 3100, 1630, 1610, 1485 cm^{-1}

NMR (DMSO-d_6, δ) : 7.39 (1H, s), 7.6-7.8 (4H, m)

MASS (m/z) : 215 (M)

Anal. Calcd. for $C_6H_5N_3S_3$: C 33.49, H 2.33, N 19.53

Found : C 33.65, H 2.24, N 19.36

(12) 2-Amino-5-(2-thiazolin-2-ylthio)thiazole

mp : 137-139°C

IR (Nujol) : 3270, 3120, 1630, 1605, 1560, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 3.33 (2H, t, J=8Hz), 4.22 (2H, t, J=8Hz), 7.24 (1H, s), 7.59 (2H, s)

MASS (m/z) : 217 (M)

Anal. Calcd. for $C_6H_7N_3S_3$: C 33.18, H 3.23, N 19.35

Found : C 33.30, H 3.11, N 18.97

(13) 2-Amino-5-(1,2,4-triazol-3-ylthio)thiazole

mp : 230-232°C (dec.)

IR (Nujol) : 3400, 3220, 3150, 1610, 1520, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 7.17 (1H, s), 7.38 (2H, s), 8.44 (1H, s), 14.09 (1H, s)

MASS (m/z) : 199 (M)

(14) 2-Amino-5-(5-amino-1,2,4-triazol-3-ylthio)thiazole

mp : 212-215°C (dec.)

IR (Nujol) : 3300, 3150, 1655, 1620, 1595, 1505 cm^{-1}

NMR (DMSO-d_6, δ) : 6.11 (2H, s), 7.08 (1H, s), 7.30 (2H, s), 12.00 (1H, s)

MASS (m/z) : 215 (M+1)

(15) 2-Acetylamino-5-(1,2,3-thiadiazol-5-ylthio)thiazole

mp : 180-183°C (dec.)

IR (Nujol) : 3150, 1685, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 2.13 (3H, s), 7.17 (1H, d, J=3.5Hz), 7.45 (1H, d, J=3.5Hz), 12.07 (1H, s)

MASS (m/z) : 257 (M-1)

(16) 2-(2-Amino-5-thiazolylthio)pyridine N-oxide

mp : 208-210°C (dec.)

IR (Nujol) : 3300, 3150, 1630, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 6.92 (1H, dd, J=2, 8Hz), 7.2-7.4 (2H, m), 7.31 (1H, s), 7.67 (2H, s), 8.32 (1H, dd, J=1, 6Hz)

MASS (m/z) : 226 (M+1)

(17) 2-Amino-4-(2-quinolylthiomethyl)thiazole

mp : 104-105°C

IR (Nujol) : 3350, 1615, 1585, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 4.40 (2H, s), 6.50 (1H, s), 6.96 (2H, s), 7.37 (1H, d, J=8Hz), 7.4-8.0 (4H, m), 8.17 (1H, d, J=8Hz)

MASS (m/z) : 274 (M+1)

Anal. Calcd. for $C_{13}H_{11}N_3S_2$: C 57.14, H 4.03, N 15.38

Found : C 57.29, H 4.07, N 15.30

Example 3

A solution of 3-chloroperbenzoic acid (1 g) in dichloromethane (10 ml) was added dropwise to an ice-cooled solution of 2-amino-5-(2-quinolylthio)thiazole (1.2 g) in dichloromethane (20 ml). The mixture was stirred at 5°C for 3 hours and the reaction was quenched with an aqueous solution of sodium bisulfite. The organic layer was separated, washed with a sodium bicarbonate solution, dried, and concentrated under reduced pressure. The residue was recrystallized from a mixture of isopropanol and ethanol to give crystals of 2-amino-5-(2-quinolylsulfinyl)thiazole (1.0 g).

mp : 178-180°C

IR (Nujol) : 3300, 1640, 1580, 1520 cm^{-1}

NMR (DMSO-d_6, δ) : 7.6-8.2 (7H, m), 7.81 (1H, s), 8.72 (1H, d, J=8Hz)

MASS (m/z) : 276 (M+1)

Anal. Calcd. for $C_{12}H_9N_3OS_2 \cdot 1/5H_2O$:
C 51.69, H 3.37, N 15.08

Found : C 51.59, H 3.30, N 14.73

Example 4

The following compounds were obtained according to a similar manner to that of Example 2.

(1) 2-Amino-5-(2-quinoxalinylsulfinyl)thiazole

mp : 175-180°C (dec.)

IR (Nujol) : 3300, 1625, 1520 cm^{-1}

NMR (DMSO-d_6, δ) : 7.89 (1H, s), 7.9-8.3 (6H, m), 9.39 (1H, s)

MASS (m/z) : 277 (M+1)

(2) 2-Amino-5-(1,8-naphthyridin-2-ylsulfinyl)thiazole

mp : 210-212°C (dec.)
IR (Nujol) : 3300, 1645, 1585, 1525 cm^{-1}
NMR (DMSO-d_6, δ) : 7.7-7.8 (1H, m), 7.85 (3H, s), 8.23 (1H, d, J=8Hz), 8.6-8.7 (1H, m), 8.84 (1H, d, J=8Hz), 9.1-9.2 (1H, m)
MASS (m/z) : 277 (M+1)
Anal. Calcd. for $C_{11}H_8N_4OS_2 \cdot 1/2H_2O$: C 46.47, H 3.17, N 19.71
Found : C 46.90, H 2.89, N 19.22

(3) 2-Amino-5-(6-methyl-2-quinolylsulfinyl)thiazole
mp : 194-195°C (dec.)
IR (Nujol) : 3420, 3280, 1630, 1580, 1525 cm^{-1}
NMR (DMSO-d_6, δ) : 2.53 (3H, s), 7.6-8.0 (6H, m), 8.05 (1H, d, J=8Hz), 8.60 (1H, d, J=8Hz)
MASS (m/z) : 290 (M+1)
Anal. Calcd. for $C_{13}H_{11}N_3OS_2$: C 53.98, H 3.81, N 14.53
Found : C 54.22, H 3.73, N 14.32

(4) 2-Amino-5-(6-fluoro-2-quinolylsulfinyl)thiazole
mp : 200-202°C (dec.)
IR (Nujol) : 3250, 1625, 1585, 1565, 1530, 1490 cm^{-1}
NMR (DMSO-d_6, δ) : 7.7-8.2 (7H, m), 8.71 (1H, d, J=8Hz)
MASS (m/z) : 294 (M+1)
Anal. Calcd. for $C_{12}H_8FN_3OS_2$: C 49.15, H 2.73, N 14.33
Found : C 49.41, H 2.58, N 14.07

(5) 2-Amino-5-(8-quinolylsulfinyl)thiazole
mp : 192-194°C (dec.)
IR (Nujol) : 3300, 1620, 1520, 1485 cm^{-1}
NMR (DMSO-d_6, δ) : 7.53 (2H, s), 7.6-7.7 (1H, m), 7.67 (1H, s), 7.8-8.0 (1H, m), 8.1-8.6 (3H, m), 8.8-9.0 (1H, m)
MASS (m/z) : 275 (M)

Anal. Calcd. for $C_{12}H_9N_3OS_2$: C 52.36, H 3.27, N 15.27
Found : C 52.71, H 3.46, N 14.76

(6) 2-Amino-5-(2-benzimidazolylsulfinyl)thiazole
mp : 189-191°C (dec.)
IR (Nujol) : 3420, 3270, 1610, 1510 cm^{-1}
NMR (DMSO-d_6 δ) : 7.2-7.4 (2H, m), 7.5-7.7 (2H, m), 7.86 (1H, s), 7.98 (2H, s), 13.47 (1H, s)
MASS (m/z) : 216
Anal. Calcd. for $C_{10}H_8N_4OS_2$: C 45.45, H 3.03, N 21.21
Found : C 45.21, H 3.03, N 20.70

(7) 2-Amino-5-(2-thienylsulfinyl)thiazole
mp : 150-152°C
IR (Nujol) : 3300, 3100, 1625, 1520, 1480 cm^{-1}
NMR (DMSO-d_6, δ) : 7.1-7.2 (1H, m), 7.4-7.5 (1H, m), 7.69 (1H, s), 7.9-8.0 (3H, m)
MASS (m/z) : 230 (M), 182
Anal. Calcd. for $C_7H_6N_2OS_3$: C 36.52, H 2.61, N 12.17
Found : C 36.68, H 2.47, N 11.63

(8) 2-Acetylamino-5-(5-bromo-2-thienylsulfinyl)thiazole
mp : 155-156°C
IR (Nujol) : 3150, 1690, 1540 cm^{-1}
NMR (DMSO-d_6, δ) : 2.18 (3H, s), 7.36 (1H, d, J=4Hz), 7.45 (1H, d, J=4Hz), 8.14 (1H, s), 12.68 (1H, s)
MASS (m/z) : 351 (M)

(9) 2-Amino-5-(5-bromo-2-thienylsulfinyl)thiazole
mp : 173-175°C
IR (Nujol) : 3350, 1620, 1515 cm^{-1}
NMR (DMSO-d_6 δ) : 7.2-7.4 (2H, m), 7.72 (1H, s), 8.00 (2H, s)
MASS (m/z) : 308 (M), 292, 260
Anal. Calcd. for $C_7H_5BrN_2OS_3$: C 27.18, H 1.62, N 9.06

Found : C 27.03, H 1.51, N 8.87

(10) 2-Amino-5-(2-thiazolylsulfinyl)thiazole

mp : 178-180°C

IR (Nujol) : 3270, 1640, 1525 cm^{-1}

NMR (DMSO-d_6, δ) : 7.86 (1H, s), 8.0-8.2 (4H, m)

MASS (m/z) : 231 (M), 215, 183

Anal. Calcd. for $C_6H_5N_3OS_3$: C 31.17, H 2.16, N 18.18

Found : C 31.54, H 2.06, N 17.76

(11) Bis(2-amino-5-thiazolyl)sulfoxide

mp : 210-215°C (dec.)

IR (Nujol) : 3250, 3150, 1615 cm^{-1}

NMR (DMSO-d_6 δ) : 7.45 (2H, s), 7.80 (4H, s)

MASS (m/z) : 247 (M+1)

(12) 2-(2-Amino-5-thiazolylsulfinyl)pyridine N-oxide

mp : 185-187°C (dec.)

IR (Nujol) : 3300, 1620, 1585, 1535 cm^{-1}

NMR (DMSO-d_6, δ) : 7.6-8.0 (3H, m), 7.70 (1H, s), 7.78 (2H, s), 8.3-8.4 (1H, m)

MASS (m/z) : 242 (M+1)

(13) 2-Amino-4-(2-quinolylsulfinylmethyl)thiazole

mp : 169-170°C (dec.)

IR (Nujol) : 3400, 3300, 1610, 1580, 1520 cm^{-1}

NMR (DMSO-d_6, δ) : 3.99 (1H, d, J=13Hz), 4.24 (1H, d, J=13Hz), 6.42 (1H, s), 7.01 (2H, s), 7.7-8.2 (5H, m), 8.69 (1H, d, J=8Hz)

MASS (m/z): 290 (M+1)

Anal. Calcd. for $C_{13}H_{11}N_3OS_2 \cdot 1/2H_2O$:

C 52.52, H 4.04, N 14.14

Found : C 52.71, H 3.94, N 13.76

(14) 2-Amino-5-(4-quinazolinylsulfinyl)thiazole

mp : 145-148°C

NMR (DMSO-d_6, δ): 7.23 (1H, s), 7.4-8.3 (6H, m), 8.42 (1H, s)

MASS (m/z) : 277 (M+1)

Example 5

A mixture of 2-amino-5-(2-quinolylthio)thiazole (0.8 g) and 3-chloroperbenzoic acid (1.5 g) in dichloromethane (100 ml) was stirred at room temperature for 5 hours. The mixture was washed with a sodium bicarbonate solution, dried, and concentrated under reduced pressure. The residue was recrystallized from ethanol to give crystals of 2-amino-5-(2-quinolylsulfonyl)thiazole (0.81 g).

mp : 198-200°C

IR (Nujol) : 3400, 3300, 1640, 1580, 1520 cm^{-1}

NMR (DMSO-d_6, δ) : 7.77 (1H, s), 7.7-8.2 (7H, m), 8.74 (1H, d, J=8Hz)

MASS (m/z) : 292 (M+1)

Anal. Calcd. for $C_{12}H_9N_3O_2S_2$: C 49.48, H 3.09, N 14.43

Found : C 49.31, H 3.36, N 14.00

Example 6

The following compounds were obtained according to a similar manner to that of Example 5.

(1) 2-Amino-5-(2-quinoxalinylsulfonyl)thiazole

mp : 175-180°C (dec.)

IR (Nujol) : 3300, 1660, 1535, 1485 cm^{-1}

NMR (DMSO-d_6, δ) : 7.87 (1H, s), 8.0-8.4 (6H, m), 9.55 (1H, s)

MASS (m/z) : 293 (M+1)

Anal. Calcd. for $C_{11}H_8N_4O_2S_2$: C 45.21, H 2.74, N 18.18

Found : C 45.81, H 3.09, N 18.05

(2) 2-Amino-5-(6-methyl-2-quinolylsulfonyl)thiazole

mp : 219-220°C (dec.)
IR (Nujol) : 3420, 1630, 1580, 1530 cm^{-1}
NMR (DMSO-d_6, δ) : 2.55 (3H, s), 7.76 (1H, s), 7.78 (1H, d, J=8Hz), 7.9-8.2 (5H, m), 8.61 (1H, d, J=8Hz)
MASS (m/z) : 306 (M+1)
Anal. Calcd. for $C_{13}H_{11}N_3O_2S_2$: C 51.15, H 3.61, N 13.77
Found : C 51.63, H 3.74, N 13.46

(3) 2-Amino-5-(6-fluoro-2-quinolylsulfonyl)thiazole
mp : 195°C (dec.)
IR (Nujol) : 3400, 1625, 1520, 1485 cm^{-1}
NMR (DMSO-d_6, δ) : 7.78 (1H, s), 7.8-8.3 (6H, m), 8.73 (1H, d, J=8Hz)
MASS (m/z) : 310 (M+1)
Anal. Calcd. for $C_{12}H_8FN_3O_2S_2$: C 46.60, H 2.59, N 13.59
Found : C 47.16, H 2.61, N 13.30

(4) 2-Amino-5-(8-quinolylsulfonyl)thiazole
mp : 220-225°C (dec.)
IR (Nujol) : 3350, 1620, 1560, 1530 cm^{-1}
NMR (DMSO-d_6, δ) : 7.6-8.0 (5H, m), 8.3-8.6 (3H, m), 9.0-9.2 (1H, m)
MASS (m/z) : 292 (M+1)
Anal. Calcd. for $C_{12}H_9N_3O_2S_2 \cdot 1/10iPA$:
C 49.70, H 3.30, N 14.14
Found : C 49.61, H 3.47, N 13.74

(5) 2-Amino-5-(2-benzimidazolylsulfonyl)thiazole
mp : 245°C (dec.)
IR (Nujol) : 3450, 3250, 1620, 1510 cm^{-1}
NMR (DMSO-d_6, δ) : 7.3-7.4 (2H, m), 7.6-7.7 (2H, m), 7.80 (1H, s), 8.29 (2H, s), 13.92 (1H, s)
Mass (m/z) : 280 (M)
Anal. Calcd. for $C_{10}H_8N_4O_2S_2 \cdot 1/5iPA$:

C 43.50, H 3.28, N 19.18
Found : C 43.88, H 3.34, N 18.85

(6) 2-Amino-5-(2-thienylsulfonyl)thiazole
mp : 220-222°C
IR (Nujol) : 3450, 1635, 1530, 1480 cm^{-1}
NMR (DMSO-d_6, δ) : 7.1-7.3 (1H, m), 7.66 (1H, s), 7.7-7.8 (1H, m), 8.0-8.1 (1H, m), 8.13 (2H, s)
MASS (m/z) : 246 (M)
Anal. Calcd. for $C_7H_6N_2O_2S_3$: C 34.15, H 2.44, N 11.38
Found : C 34.53, H 2.35, N 10.95

(7) 2-Amino-5-(2-thiazolylsulfonyl)thiazole
mp : 193-195°C
IR (Nujol) : 3280, 1645, 1525 cm^{-1}
NMR (DMSO-d_6, δ) : 7.80 (1H, s), 8.10 (1H, d, J=3Hz), 8.21 (1H, d, J=3Hz), 8.34 (2H, s)
MASS (m/z) : 247 (M)
Anal. Calcd. for $C_6H_5N_3O_2S_3 \cdot 1/10C_4H_8O$:
C 30.31, H 2.28, N 16.54
Found : C 30.21, H 2.18, N 16.24

Example 7

A mixture of 2-amino-5-(5-nitro-2-benzimidazolylthio)thiazole (1 g), iron powder (1 g), ammonium chloride (0.5 g), tetrahydrofuran (10 ml), and water (10 ml) in ethanol (30 ml) was stirred under reflux for 2 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was pulverized in an ice-water and the crude powder was purified by column chromatography eluting with a mixture of chloroform and methanol (5:1) to give a pale yellow powder of 2-amino-5-(5-amino-2-benzimidazolylthio)thiazole (0.75 g).

mp : 195-197°C (dec.)
IR (Nujol) : 3300, 1625, 1520 cm^{-1}

NMR (DMSO-d_6, δ) : 4.91 (2H, s), 6.4-6.6 (2H, m), 7.15 (1H, d, J=8Hz), 7.25 (1H, s), 7.47 (2H, s), 11.84 (1H, s)

MASS (m/z) : 263 (M)

Anal. Calcd. for $C_{10}H_9N_5S_2 \cdot 1/5H_2O$) :
C 45.01, H 3.53, N 26.25

Found : C 45.31, H 3.52, N 25.92

Example 8

Acetyl chloride (1.8 g) was added dropwise to an ice-cooled solution of 2-amino-5-(2-thienylthio)thiazole (4 g) in pyridine (80 ml). The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in a mixture of tetrahydrofuran and ethyl acetate and washed with dilute hydrochloric acid and water, successively. The organic layer was dried and evaporated to give a yellow powder of 2-acetylamino-5-(2-thienylthio)thiazole (4.5 g).

mp : 180-182°C (dec.)

IR (Nujol) : 3150, 1695, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 2.14 (3H, s), 7.0-7.1 (1H, m), 7.2-7.4 (1H, m), 7.6-7.7 (1H, m), 7.68 (1H, s), 12.32 (1H, s)

MASS (m/z) : 256 (M)

Example 9

Bromine (3 g) in dichloromethane (10 ml) was added dropwise to an ice-cooled solution of 2-(acetylamino)-5-(2-thienylthio)thiazole (3.8 g) in a mixture of acetic acid (30 ml) and dichloromethane (60 ml). The mixture was stirred at room temperature for 6 hours and concentrated under reduced pressure. Ice-water was added to the residue and the mixture was neutralized with sodium bicarbonate. The precipitates were collected and washed to give a powder of 2-acetylamino-5-(5-bromo-2-thienylthio)thiazole (4.1 g).

mp : 160-163°C (dec.)
IR (Nujol) : 3400, 1695, 1565 cm^{-1}
NMR (DMSO-d_6, δ) : 2.15 (3H, s), 7.1-7.3 (2H, m), 7.71 (1H, s), 12.38 (1H, s)
MASS (m/z) : 335 (M)

Example 10

A mixture of 2-acetylamino-5-(5-bromo-2-thienylthio)thiazole (2 g) and conc. hydrochloric acid (10 ml) in ethanol (50 ml) was refluxed for 5 hours. The solvent was evaporated and ice-water was added to the residue. The mixture was neutralized with sodium bicarbonate and extracted with a mixture of tetrahydrofuran and ethyl acetate. The extract was washed with water, dried, and evaporated to give a solid of 2-amino-5-(5-bromo-2-thienylthio)thiazole (1.8 g).

mp : 210-215°C (dec.)
NMR (DMSO-d_6, δ) : 7.05 (1H, d, J=4Hz), 7.13 (1H, d, J=4Hz), 7.21 (1H, s), 7.48 (2H, s)
MASS (m/z) : 293 (M)

Example 11

The following compounds were obtained according to a similar manner to that of Example 10.

(1) 2-Amino-5-(1,2,4-triazol-3-ylsulfonyl)thiazole
mp : 247-250°C (dec.)
IR (Nujol) : 3400, 3150, 1620, 1500 cm^{-1}
NMR (DMSO-d_6, δ) : 7.68 (1H, s), 8.22 (2H, s), 8.78 (1H, s)
MASS (m/z) : 232 (M+1)

(2) 2-Amino-5-(5-amino-1,2,4-triazol-3-ylsulfonyl)thiazole
mp : 278-280°C (dec.)
IR (Nujol) : 3450, 3380, 3250, 3180, 1640, 1580,

1530 cm^{-1}

NMR (DMSO-d_6, δ) : 6.52 (2H, s), 7.59 (1H, s), 8.10 (2H, s), 12.80 (1H, s)

MASS (m/z) : 247 (M+1)

Anal. Calcd. for $C_5H_6N_6O_2S_2 \cdot 1/10H_2O$: C 24.22, H 2.50, N 33.80

Found : C 24.62, H 2.50, N 33.09

(3) 2-Amino-5-(1,2,3-thiadiazol-5-ylthio)thiazole

mp : 116-118°C

NMR (DMSO-d_6, δ) : 7.42 (1H, s), 7.74 (2H, s), 8.76 (1H, s)

MASS (m/z) : 217 (M+1)

Anal. Calcd. for $C_5H_4N_4S_3 \cdot 1/10iPE$) : C 29.10, H 2.14, N 25.00

Found : C 29.51, H 2.03, N 24.69

(4) 2-Amino-5-(1,2,3,-thiadiazol-5-ylsulfonyl)thiazole

mp : 170-173°C (dec.)

IR (Nujol) : 3450, 1630, 1520 cm^{-1}

NMR (DMSO-d_6, δ) : 7.92 (1H, s), 8.50 (2H, s), 9.53 (1H, s)

MASS (m/z) : 247 (M-1)

Anal. Calcd. for $C_5H_4N_4O_2S_3 \cdot 1/3iPA$: C 26.80, H 2.51, N 20.90

Found : C 26.28, H 2.04, N 20.39

(5) Bis(2-amino-5-thiazolyl)sulfide

mp : 165-168°C

IR (Nujol) : 3420, 1620, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 7.06 (2H, s), 7.30 (4H, s)

MASS (m/z) : 230 (M)

Example 12

Acetyl chloride (2 g) was added dropwise to an ice-

cooled solution of 2-amino-5-(1,2,4-triazol-3-ylthio)thiazole (1.7 g) in pyridine (100 ml). The reaction mixture was stirred at 5°C for 1.5 hours and concentrated under reduced pressure. Water was added to the residue and the mixture was acidified with HCl. The precipitates were collected, washed with water, and dried to give a powder of 2-acetylamino-5-(1-acetyl-1,2,4-triazol-3-ylthio)thiazole (1.7 g).

mp : 249-252°C (dec.)

IR (Nujol) : 3150, 1745, 1700, 1560, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 2.17 (3H, s), 2.58 (3H, s), 7.78 (1H, s), 9.28 (1H, s), 12.44 (1H, s)

MASS (m/z) : 284 (M+1), 242

Example 13

The following compound was obtained according to a similar manner to that of Example 12.

2-Acetylamino-5-(5-acetylamino-1,2,4-triazol-3-ylthio)thiazole

mp : 305-308°C (dec.)

IR (Nujol) : 3450, 3150, 1720, 1705, 1650, 1560, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 2.19 (3H, s), 2.43 (3H, s), 7.67 (2H, s), 7.70 (1H, s), 12.37 (1H, s)

MASS (m/z) : 299 (M+1)

Example 14

A mixture of 2-acetylamino-5-(1-acetyl-1,2,4-triazol-3-ylthio)thiazole (0.5 g), hydrogen peroxide (30%; 1 ml) and sulfuric acid (2 drops) in acetic acid (10 ml) was stirred at 55°C for 1 hour. The mixture was poured into ice-water and extracted with a mixture of tetrahydrofuran and ethyl acetate. The extract was washed with water, dried, and evaporated to give a pink powder of 2-acetylamino-5-(1-

acetyl-1,2,4-triazol-3-ylsulfonyl)thiazole (0.45 g).

mp : 270-273°C (dec.)

IR (Nujol) : 3300, 3150, 1700, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 1.36 (3H, s), 2.21 (3H, s), 8.22 (1H, s), 8.85 (1H, s)

MASS (m/z) : 316 (M), 274

Example 15

The following compounds were obtained according to a similar manner to that of Example 14.

(1) 2-Acetylamino-5-(5-amino-1,2,4-triazol-3-ylsulfonyl)thiazole

mp : 273-275°C (dec.)

IR (Nujol) : 3400, 3150, 1705, 1640, 1570, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.21 (3H, s), 6.58 (2H, s), 8.11 (1H, s), 12.82 (1H, s), 12.90 (1H, s)

MASS (m/z) 289 (M+1)

(2) 2-Acetylamino-5-(1,2,3-thiadiazol-5-ylsulfonyl)-thiazole

mp : 225°C (dec.)

IR (Nujol) : 3150, 1705, 1545 cm^{-1}

NMR (DMSO-d_6, δ) : 2.23 (3H, s), 8.45 (1H, s), 9.64 (1H, s), 13.06 (1H, s)

MASS (m/z) : 289 (M-1)

Example 16

A mixture of 2-acetylamino-5-bromothiazole (3 g) and sodium hydrosulfide hydrate (3 g) in N,N-dimethylfromamide (30 ml) was stirred at 100°C for 3 hours. The reaction mixture was poured into dilute hydrochloric acid and the precipitates were collected, washed with water, and dried to give a powder of bis(2-acetylamino-5-thiazolyl)sulfide (2.35 g).

mp : 175-180°C (dec.)
NMR ($CDCl_3$-DMSO-d_6, δ) : 2.10 (6H, s), 7.50 (2H, s)
MASS (m/z) : 314 (M)

Example 17

A mixture of 2-amino-5-(2-quinolylthio)thiazole (2.3 g) and isoamyl nitrite (1.6 g) in tetrahydrofuran (50 ml) was stirred under reflux for 3 hours. The solvent was evaporated, and the residue was dissolved in a mixture of tetrahydrofuran and ethyl acetate and washed with water. The organic extract was dried and evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with a mixture of dichloromethane and ethanol (10:1) to give a solid of 5-(2-quinolylthio)thiazole (1.55 g).

mp : 60-63°C
IR (Nujol) : 1580, 1555, 1495 cm^{-1}
NMR (DMSO-d_6, δ) : 7.28 (1H, d, J=9Hz), 7.5-8.0 (4H, m), 8.26 (1H, s), 8.30 (1H, d, J=9Hz), 9.47 (1H, s)
MASS (m/z) : 245 (M+1)
Anal. Calcd. for $C_{12}H_8N_2S_2$: C 59.02, H 3.28, N 11.48
Found : C 58.59, H 3.33, N 11.33

Example 18

The following compounds were obtained according to a similar manner to that of Example 17.

(1) 5-(2-Pyridylthio)thiazole (oil)
IR (Film) : 1575, 1560 cm^{-1}
NMR ($CDCl_3$, δ) : 6.9-7.2 (2H, m), 7.4-7.6 (1H, m), 8.07 (1H, s), 8.4-8.5 (1H, m), 9.03 (1H, s)
MASS (m/z) : 195 (M+1)

(2) Di(5-thiazolyl)sulfide
IR (Film) : 3100, 2950, 1475 cm^{-1}
NMR ($CDCl_3$, δ) : 7.97 (2H, s), 8.85 (2H, s)

MASS (m/z) : 201 (M+1)

Example 19

A solution of 3-chloroperbenzoic acid (0.62 g) in dichloromethane (20 ml) was added dropwise to an ice-cooled solution of 5-(2-quinolylthio)thiazole (0.7 g) in dichloromethane (100 ml). The mixture was stirred at 5°C for 3 hours and the reaction was quenched with an aqueous solution of sodium bisulfite. The organic layer was separated, washed with a sodium bicarbonate solution, dried, and concentrated under reduced pressure. The residue was recrystallized from a mixture of isopropanol and ethanol to give crystals of 5-(2-quinolylsulfinyl)thiazole (0.72 g).

mp : 125-126°C

IR (Nujol) : 1580, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 7.7-8.2 (5H, m), 8.63 (1H, s), 8.78 (1H, d, J=8Hz), 9.40 (1H, s)

MASS (m/z) : 261 (M+1)

Anal. Calcd. for $C_{11}H_8N_2OS_2$: C 55.38, H 3.08, N 10.77

Found : C 54.94, H 3.20, N 10.65

Example 20

The following compounds were obtained according to a similar manner to that of Example 19.

(1) 5-(2-Pyridylsulfinyl)thiazole

mp : 90-91°C (EtOH)

IR (Nujol) : 1575, 1560, 1485 cm^{-1}

NMR (DMSO-d_6, δ) : 7.5-7.7 (1H, m), 8.0-8.3 (2H, m), 8.57 (1H, s), 8.6-8.7 (1H, m), 9.41 (1H, s)

MASS (m/z) : 211 (M+1)

Anal. Calcd. for $C_8H_6N_2OS_2$: C 45.71, H 2.86, N 13.33

Found : C 45.67, H 2.67, N 13.22

(2) Di(5-thiazolyl)sulfoxide

mp : 88-90°C
IR (Nujol) : 1430, 1310 cm^{-1}
NMR (DMSO-d_6, δ) : 8.49 (2H, s), 9.49 (2H, s)
MASS (m/z) : 217 (M+1)
Anal. Calcd. for $C_6H_4N_2S_3O \cdot 1/10$ toluene :
C 35.56, H 2.22, N 12.44
Found : C 35.16, H 2.14, N 11.59

(3) 2-Guanidino-5-(2-pyridylsulfinyl)thiazole
mp : 207-210°C (dec.)
IR (Nujol) : 3350, 1620, 1580, 1520 cm^{-1}
NMR (DMSO-d_6, δ) : 7.10 (4H, s), 7.5-7.6 (1H, m), 7.86 (1H, s), 7.9-8.2 (2H, m), 8.5-8.7 (1H, m)
MASS (m/z) : 268 (M+1)

(4) 2-(2-Pyridylsulfinyl)thiazole
mp : 52-53°C
IR (Nujol) : 1575 cm^{-1}
NMR (DMSO-d_6, δ) : 7.5-7.7 (1H, m), 8.0-8.3 (4H, m), 8.6-8.7 (1H, m)
MASS (m/z) : 211 (M+1)
Anal. Calcd. for $C_8H_6N_2OS_2 \cdot 1/10$ toluene :
C 47.49, H 3.20, N 12.78
Found : C 47.66, H 3.41, N 12.36

(5) 2.5-Bis(2-pyridylsulfinyl)thiazole
mp : 114-116°C (EtOH)
IR (Nujol) : 1575 cm^{-1}
NMR (DMSO-d_6, δ) : 7.6-7.7 (2H, m), 7.9-8.3 (4H, m), 8.5-8.8 (3H, m)
MASS (m/z) : 336 (M+1)
Anal. Calcd. for $C_{13}H_9N_3O_2S_2$: C 46.57, H 2.69, N 12.54
Found : C 46.08, H 2.64, N 12.25

(6) 2-(2-Acetylhydrazino)-5-(2-pyridylsulfinyl)thiazole

mp : 210-220°C (dec.)

NMR (DMSO-d_6, δ) : 1.84 (3H, s), 7.3-8.2 (4H, m), 8.4-8.5 (1H, m), 10.28 (1H, s)

MASS (m/z) : 281 (M-1)

(7) 2-Amino-5-(2-quinolylsulfinyl)-1,3,4-thiadiazole

mp : 191-192°C

IR (Nujol) : 3320, 3100, 1625, 1580, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 7.7-8.2 (7H, m), 8.80 (1H, d, J=8Hz)

MASS (m/z) : 277 (M+1)

Anal. Calcd. for $C_{11}H_8N_4OS_2$: C 47.83, H 2.90, N 20.29

Found : C 48.39, H 3.08, N 19.23

Example 21

A mixture of 5-(2-pyridylthio)thiazole (1.3 g) and 3-chloroperbenzoic acid (1.5 g) in dichloromethane (70 ml) was stirred at room temperature for 5 hours. The mixture was washed with a sodium bicarbonate solution, dried, and concentrated under reduced pressure. The residue was recrystallized from ethanol to give crystals of 5-(2-pyridylsulfonyl)thiazole (1.3 g).

mp : 108-110°C

IR (Nujol) : 1580, 1480 cm^{-1}

NMR (DMSO-d_6, δ) : 7.7-7.8 (1H, m), 8.1-8.3 (2H, m), 8.62 (1H, s), 8.7-8.8 (1H, m), 9.57 (1H, s)

MASS (m/z) : 227 (M+1)

Anal. Calcd. for $C_8H_6N_2O_2S_2$: C 42.48, H 2.65, N 12.39

Found : C 42.82, H 2.71, N 12.25

Example 22

Sodium hydride (0.22 g) was added to an ice-cooled solution of 2-(formylamino)-5-(2-pyridylsulfinyl)thiazole (1.3 g) in N,N-dimethylformamide (20 ml). The mixture was stirred at 5°C for 30 minutes. To the mixture was added

methyl iodide (0.9 g) dropwise. Then the resulting mixture was stirred at room temperature for 1 hour and concentrated to dryness. The residue was dissolved in a mixture of tetrahydrofuran and ethyl acetate and washed with water. The extract was dried and evaporated to give a yellow powder of 2-(N-formyl-N-methylamino)-5-(2-pyridylsulfinyl)thiazole (1.4 g).

NMR (DMSO-d_6, δ) : 3.52 (3H, s), 7.5-8.3 (3H, m), 8.33 (1H, s), 8.6-8.7 (1H, m), 8.72 (1H, s)

MASS (m/z) : 268 (M+1)

Example 23

The following compound was obtained according to a similar manner to that of Example 22.

2-[N-Formyl-N-(5-methyl-2-oxo-1,3-dioxol-4-ylmethyl)amino]-5-(2-pyridylsulfinyl)thiazole

mp : 144-145°C

IR (Nujol) : 1840, 1680, 1575, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 2.21 (3H, s), 5.14 (2H, s), 7.5-7.7 (1H, m), 8.0-8.15 (2H, m), 8.35 (1H, s), 8.6-8.7 (1H, m), 8.85 (1H, s)

MASS (m/z) : 366 (M+1)

Example 24

A mixture of 2-(N-formyl-N-methylamino)-5-(2-pyridylsulfinyl)thiazole (1.5 g) and conc. hydrochloric acid (8 ml) in methanol (50 ml) was stirred at room temperature for 4 hours. The mixture was concentrated and the residue was dissolved in water. The solution was made alkaline (pH 8.5) with sodium bicarbonate and extracted with a mixture of tetrahydrofuran and ethyl acetate. The extract was washed with water, dried, and concentrated to dryness. The residual oil was recrystallized from ethanol to give crystals of 2-methylamino-5-(2-pyridylsulfinyl)thiazole (0.78 g).

mp : 124-126°C

IR (Nujol) : 3200, 1610, 1580, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 2.79 (3H, d, J=5Hz), 7.5-7.6 (1H, m), 7.84 (1H, s), 7.9-8.4 (3H, m), 8.6-8.7 (1H, m)

MASS (m/z) : 240 (M+1)

Anal. Calcd. for $C_9H_9N_3OS_2$: C 45.19, H 3.77, N 17.57

Found : C 44.97, H 3.59, N 17.07

Example 25

The following compound was obtained according to a similar manner to that of Example 24.

2-(5-Methyl-2-oxo-1,3-dioxol-4-ylmethyl)amino-5-(2-pyridylsulfinyl)thiazole

IR (Nujol) : 1810, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.13 (3H, s), 4.32 (2H, d, J=5Hz), 7.5-7.6 (1H, m), 7.88 (1H, s), 7.9-8.3 (2H, m), 8.6-8.8 (2H, m)

MASS (m/z) : 338 (M+1)

Anal. Calcd. for $C_{13}H_{11}N_3O_4S_2 \cdot 1/2\ H_2O$:

C 45.09, H 3.47, N 12.14

Found : C 45.57, H 3.90, N 11.43

Example 26

Benzoyl chloride (15 g) was added dropwise to a solution of sodium thiocyanate (10 g) in acetone (500 ml) and the mixture was stirred at room temperature for 30 minutes. 2-Amino-5-(2-pyridylthio)thiazole (18 g) was added portionwise to the above mixture. The resulting mixture was stirred for 9 hours and concentrated to dryness. To the residue were added sodium carbonate (15 g), water (50 ml) and methanol (250 ml), and the mixture was stirred at 60°C for 5 hours. The solvent was evaporated and ice-water was added to the residue. The suspension was neutralized with hydrochloric acid and extracted with a mixture of

tetrahydrofuran and ethyl acetate. The extract was washed with water, dried, and evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with a mixture of chloroform and methanol (10:1) to give a solid of 2-thioureido-5-(2-pyridylthio)thiazole (11.5 g).

mp : 205-207°C (dec.)

IR (Nujol) : 3400, 3300, 1645, 1605, 1575, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 7.07 (1H, d, J=8Hz), 7.1-7.3 (1H, m), 7.6-7.9 (2H, m), 7.75 (1H, s), 8.4-8.8 (2H, m), 11.89 (1H, s)

MASS (m/z) : 269 (M+1)

Example 27

The following compound was obtained according to a similar manner to that of Example 26.

2-Thioureido-5-(2-pyridylsulfinyl)thiazole

mp : 183-185°C (dec.)

IR (Nujol) : 3300, 1620, 1570 cm^{-1}

NMR (DMSO-d_6, δ) : 7.5-7.8 (2H, m), 8.0-8.2 (2H, m), 8.19 (1H, s), 8.6-8.7 (1H, m), 8.81 (1H, s), 12.03 (1H, s)

MASS (m/z) : 285 (M+1)

Anal. Calcd. for $C_9H_8N_4OS_3$: C 38.03, H 2.82, N 19.72

Found : C 38.17, H 2.82, N 19.45

Example 28

Methyl iodide (2.3 g) was added to a suspension of 2-thioureido-5-(2-pyridylthio)thiazole (2.3 g) in ethanol (50 ml). The mixture was stirred under reflux for 9 hours and concentrated to dryness. Ice-water was added and the mixture was made alkaline (pH 8.5) with sodium bicarbonate and extracted with a mixture of tetrahydrofuran and ethyl acetate. The extract was washed with water, dried, and evaporated to give an oily residue (1.5 g). The residue was

purified by column chromatography on silica gel eluting with a mixture of chloroform and methanol (20:1) to give a yellow powder of 2-(S-methylisothioureido)-5-(2-pyridylthio)thiazole (1.1 g).

mp : 125-126°C

IR (Nujol) : 3250, 1615, 1580, 1525 cm^{-1}

NMR ($CDCl_3$, δ) : 2.51 (3H, s), 6.9-7.1 (1H, m), 7.4-7.6 (1H, m), 7.55 (1H, s), 8.4-8.5 (1H, m)

MASS (m/z) : 283 (M+1)

Example 29

A mixture of 2-(S-methylisothioureido)-5-(2-pyridylthio)thiazole (2.5 g), ammonia in ethanol (15%; 10 ml), and ethanol (25 ml) was heated at 90°C for 20 hours in a steel bomb. The solvent was evaporated and the residue was dissolved in a mixture of tetrahydrofuran and ethyl acetate and washed with water. The extract was dried and evaporated to dryness. The residue (1.6 g) was purified by column chromatography on silica gel eluting with a mixture of chloroform and methanol (40:1) to give a violet powder of 2-guanidino-5-(2-pyridylthio)thiazole (0.6 g).

mp : 175-180°C (dec.)

IR (Nujol) : 3450, 1670, 1600, 1535 cm^{-1}

NMR (DMSO-d_6, δ) : 6.9-7.2 (6H, m), 7.43 (1H, s), 7.6-7.8 (1H, m), 8.3-8.5 (1H, m)

MASS (m/z) : 252 (M+1)

Example 30

A mixture of 2-amino-5-mercapto-1,3,4-thiadiazole (1.3 g), 2-chloroquinoline (1 g) and potassium carbonate (0.81 g) in N,N-dimethylformamide (20 ml) was stirred at 105°C for 5 hours. The mixture was concentrated, and the residue was dissolved in a mixture of tetrahydrofuran and ethyl acetate and washed with water. The organic extract was dried and evaporated to dryness. The residue was purified by column

chromatography on silica gel eluting with a mixture of chloroform and methanol (10:1) to give a yellow solid of 2-amino-5-(2-quinolylthio)-1,3,4-thiadiazole (0.75 g).

mp : 186-188°C

IR (Nujol) : 3300, 3100, 1615, 1590, 1500 cm^{-1}

NMR (DMSO-d_6 δ) : 7.41 (1H, d, J=8Hz), 7.5-8.1 (6H, m), 8.35 (1H, d, J=8Hz)

MASS (m/z) : 261 (M+1)

Anal. Calcd. for $C_{11}H_8N_4S_2$: C 50.77, H 3.08, N 21.54

Found : C 50.60, H 2.96, N 21.24

Example 31

Bromine (4.5 g) was added dropwise to an ice-cooled suspension of 2-(2-acetylhydrazino)thiazole (4 g) in acetic acid (40 ml). The mixture was stirred at room temperature for 3 hours and concentrated to dryness. To the residue was added N,N-dimethylformamide (50 ml), 2-mercaptopyridine (3.4 g), sodium bicarbonate (11.5 g) and potassium carbonate (1 g). The mixture was stirred at 105°C for 3 hours and concentrated to dryness. The residue was dissolved in a mixture of tetrahydrofuran and ethyl acetate, and washed with water. The organic layer was dried and evaporated. The residue was purified by column chromatography on silica gel eluting with a mixture of chloroform and methanol (5:1) to give a brown oil of 2-(2-acetylhydrazino)-5-(2-pyridylthio)thiazole (1.4 g).

NMR (DMSO-d_6 δ) : 1.98 (3H, s), 7.0-7.3 (2H, m), 7.41 (1H, s), 7.6-7.9 (1H, m), 8.4-8.5 (1H, m), 9.84 (1H, s), 10.23 (1H, s)

MASS (m/z) : 267 (M+1)

Example 32

The following compounds were obtained according to a similar manner to that of Example 31.

(1) 2-(2-Pyridylthio)thiazole

IR (Film) : 1570, 1560, 1450, 1420 cm^{-1}

NMR ($CDCl_3$, δ) : 7.1-7.4 (2H, m), 7.48 (1H, d, J=4Hz), 7.5-7.7 (1H, m), 7.90 (1H, d, J=4Hz), 8.4-8.6 (1H, m)

MASS (m/z) : 195 (M+1)

(2) 2,5-Bis(2-pyridylthio)thiazole

mp : 66-67°C (iPA)

IR (Nujol) : 1575 cm^{-1}

NMR (DMSO-d_6, δ) : 7.1-7.5 (3H, m), 7.6-8.0 (3H, m), 8.12 (1H, s), 8.4-8.7 (2H, m)

MASS (m/z) : 304 (M+1)

Anal. Calcd. for $C_{13}H_9N_3S_3$: C 51.49, H 2.97, N 13.86

Found : C 51.39, H 2.91, N 13.71

Example 33

A mixture of 2-(2-pyridylthio)thiazole (3 g) and N-chloro-succinimide (3.3 g) in acetic acid (30 ml) was stirred at 90°C for 5 hours. The mixture was poured into ice-water and neutralized with sodium bicarbonate. The precipitates were collected, washed with water, and dried to give a powder of 5-chloro-2-(2-pyridylthio)thiazole (2.7 g).

mp : 50-52°C

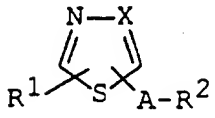
IR (Nujol) : 1580, 1560, 1495 cm^{-1}

NMR (DMSO-d_6, δ): 7.3-7.5 (1H, m), 7.56 (1H, d, J=8Hz), 7.8-7.9 (1H, m), 7.95 (1H, s), 8.5-8.7 (1H, m)

MASS (m/z) : 229 (M+1)

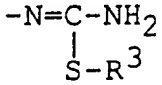
C L A I M S

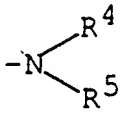
1. A compound of the formula :



wherein

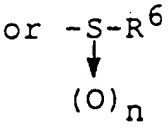
R^1 is hydrogen, halogen, amino, acylamino, thioureido, guanidino,

 (wherein R^3 is lower alkyl),



(wherein R^4 is acylamino or lower alkyl which may have suitable substituent(s) and

R^5 is hydrogen or acyl),

or 

(wherein R^6 is N-containing unsaturated heterocyclic group and

n is an integer of 0, 1 or 2),

R^2 is N- or S-containing unsaturated heterocyclic group, each of which may have suitable substituent(s),

X is CH or N and

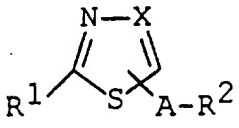
A is -S- or $-CH_2S-$ (wherein m is an integer of 0, 1 or 2),
($(O)_m$ for both)

provided that R^2 is quinolyl, quinoxalinyl, quinazolinyl, naphthyridinyl, benzimidazolyl, purinyl, thienyl, thiazolyl, thiazolinyl, triazolyl, pyridyl N-oxide or 1,2,3-thiadiazolyl, each of which may be substituted with lower alkyl, lower alkylthio, halogen, nitro, amino, acyl or acylamino,

when X is CH and R^1 is amino or acylamino,

and pharmaceutically acceptable salts thereof.

2. A compound of the formula according to claim 1,



wherein

R^1 is amino or acylamino,

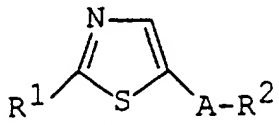
X is CH,

A is -S- or $-CH_2S-$ (wherein m is an integer of 0, 1 or 2),
($(O)_m$ for both)

and

R^2 is quinolyl, quinoxalinyl, quinazolinyl, naphthyridinyl, benzimidazolyl, purinyl, thienyl, thiazolyl, thiazolinyl, triazolyl, pyridyl N-oxide or 1,2,3-thiadiazolyl, each of which may be substituted with lower alkyl, lower alkylthio, halogen, nitro, amino, acyl or acylamino.

3. A compound of the formula according to claim 2,



wherein

R^1 is amino,

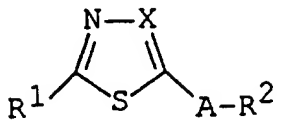
A is $-S-$ (wherein m is an integer of 0, 1 or 2) and
$(O)_m$

R^2 is quinol-2-yl, quinol-8-yl, quinoxalinyl, quinazolinyl, naphthyridinyl, benzimidazol-2-yl, purinyl, thienyl, thiazol-5-yl, thiazolinyl, 1H-1,2,4-thiazol-3-yl, pyridyl N-oxide or 1,2,3-thiadiazolyl, each of which may be substituted with lower alkyl, lower alkylthio, halogen, nitro, amino, lower alkanoyl or lower alkanoylamino.

4. A compound according to claim 3, wherein

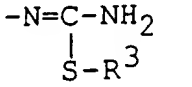
R^2 is quinol-2-yl, quinol-8-yl, quinoxalinyl, benzimidazol-2-yl, thiazolinyl, or thiazol-5-yl which may be substituted with amino.

5. A compound of the formula according to claim 1,

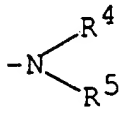


wherein

R^1 is hydrogen, halogen, thioureido, guanidino,

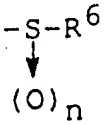


(wherein R^3 is lower alkyl),



(wherein R^4 is acylamino or lower alkyl which may have suitable substituent(s) and

R^5 is hydrogen or acyl),

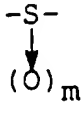
or 

(wherein R^6 is pyridyl and

n is an integer of 0, 1 or 2),

R^2 is N-containing unsaturated heterocyclic group,

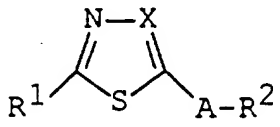
X is CH and

A is  (wherein m is an integer of 0, 1 or 2).

6. A compound according to claim 5, wherein
R^1 is hydrogen and
R^2 is unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms, unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, or unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms.

7. A compound according to claim 6, wherein
R^2 is pyridyl, thiazolyl or quinolyl.

8. A compound of the formula according to claim 1,



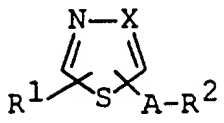
wherein
R^1 is amino,
X is N,

A is $-S-_{(O)_m}$ (wherein m is an integer of 0, 1 or 2) and

R^2 is unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms.

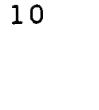
9. A compound according to claim 8,
wherein R^2 is quinolyl.

10. A process for preparing a compound of the formula :

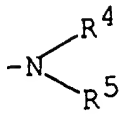


wherein

R^1 is hydrogen, halogen, amino, acylamino, thioureido, guanidino,

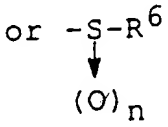


(wherein R^3 is lower alkyl),



(wherein R^4 is acylamino or lower alkyl which may have suitable substituent(s) and

R^5 is hydrogen or acyl),



(wherein R^6 is N-containing unsaturated heterocyclic group and

n is an integer of 0, 1 or 2),

R^2 is N- or S-containing unsaturated heterocyclic group, each of which may have suitable substituent(s),

X is CH or N and

A is $-S-$ or $-CH_2S-$ (wherein m is an integer of 0, 1 or 2),

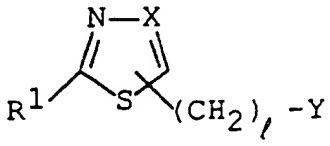
provided that R^2 is quinolyl, quinoxalinyl, quinazolinyl, naphthyridinyl, benzimidazolyl, purinyl, thienyl, thiazolyl, thiazolinyl, triazolyl, pyridyl N-oxide or 1,2,3-thiadiazolyl, each of which may be substituted with lower alkyl, lower alkylthio, halogen, nitro, amino, acyl or acylamino,

when X is CH and R^1 is amino or acylamino,

or pharmaceutically acceptable salts thereof,

which comprises

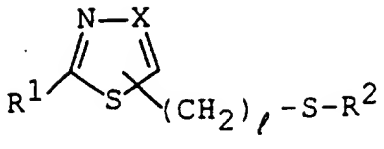
(1) reacting a compound of the formula :



or its salt with a compound of the formula :

$$R^2 - SH$$

or its salt to give a compound of the formula :



or its salt,

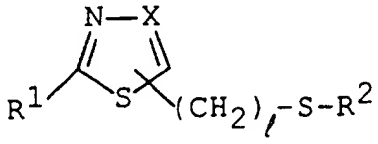
in which R^1, R^2 and X are each as defined above,

Y is halogen and

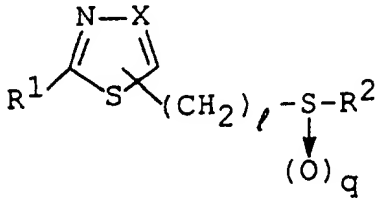
ℓ is an integer of 0 or 1,

or

(2) subjecting a compound of the formula :



or its salt to oxidation to give a compound of the formula :



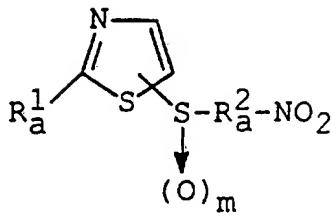
or its salt,

in which R^1, R^2, X and ℓ are each as defined above and

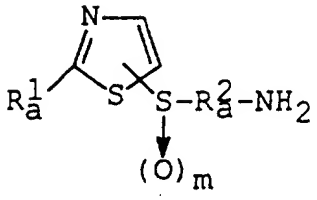
q is an integer of 1 or 2,

or

(3) reducing a compound of the formula :



or its salt to give a compound of the formula :



or its salt,

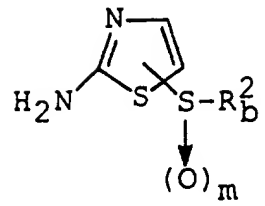
in which m is as defined above,

R_a^1 is amino or acylamino and

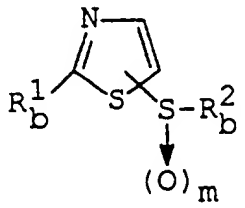
R_a^2 is quinolyl, quinoxalinyl, quinazolinyl, naphthyridinyl, benzimidazolyl, purinyl, thienyl, thiazolyl, thiazolinyl, triazolyl, pyridyl N-oxide or 1,2,3-thiadiazolyl,

or

(4) acylating a compound of the formula :



or its reactive derivative at the amino group or a salt thereof to give a compound of the formula :



or its salt,

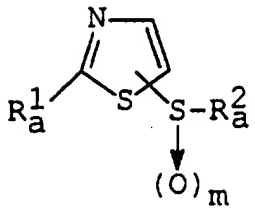
in which m is as defined above,

R_b^1 is acylamino and

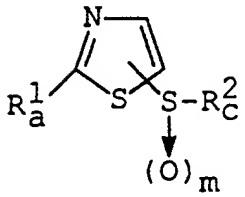
R_b^2 is quinolyl, quinoxalinyl, quinazolinyl, naphthyridinyl, benzimidazolyl, purinyl, thienyl, thiazolyl, thiazolinyl, triazolyl, pyridyl N-oxide or 1,2,3-thiadiazolyl, each of which may be substituted with lower alkyl, lower alkylthio, halogen, nitro, amino, acyl or acylamino,

or

(5) halogenating a compound of the formula :



or its salt to give a compound of the formula :



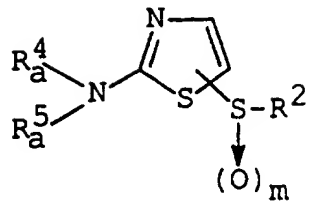
or its salt,

in which R_a^1, R_a^2 and m are each as defined above, and

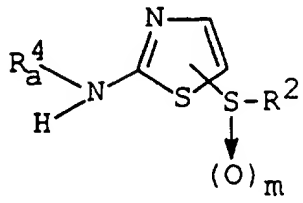
R_c^2 is quinolyl, quinoxalinyl, quinazolinyl, naphthyridinyl, benzimidazolyl, purinyl, thienyl, thiazolyl, thiazolinyl, triazolyl, pyridyl, N-oxide or 1,2,3-thiadiazolyl, each of which has halogen,

or

(6) deacylating a compound of the formula :



or its salt to give a compound of the formula :



or its salt,

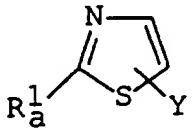
in which R^2 and m are each as defined above,

R_a^4 is hydrogen or lower alkyl which may have suitable substituent(s), and

R_a^5 is acyl,

or

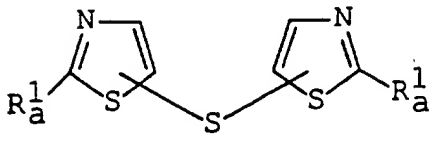
(7) reacting a compound of the formula :



or its salt with a compound of the formula :

H-S-H

or its salt to give a compound of the formula :

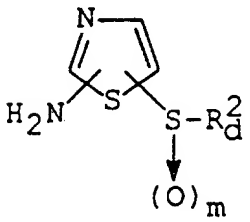


or its salt,

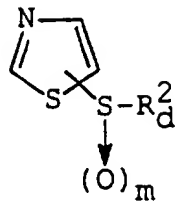
in which R_a^1 and Y are each as defined above,

or

(8) subjecting a compound of the formula :



or its reactive derivatives at the amino group or a salt thereof to deamination to give a compound of the formula :



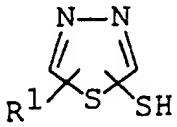
or its salt,

in which m is as defined above, and

R^2_d is N-containing unsaturated heterocyclic group,

or

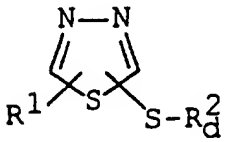
(9) reacting a compound of the formula :



or its salt with a compound of the formula :

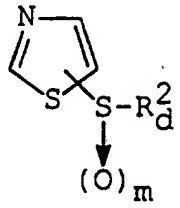
$$R^2_d\text{-}Y$$

or its salt to give a compound of the formula :

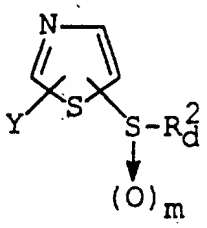


or its salt,
in which R^1, R^2_d and Y are each as defined above,
or

(10) subjecting a compound of the formula :

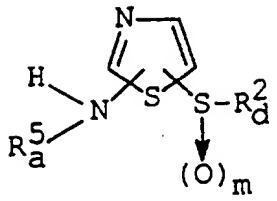


or its salt to halogenation to give a compound of the formula :

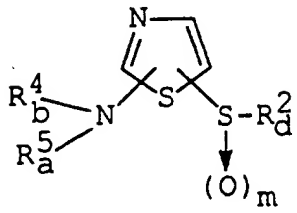


or its salt,
in which R^2_d, m and Y are each as defined above,
or

(11) subjecting a compound of the formula :



or its salt to alkylation to give a compound of the formula :



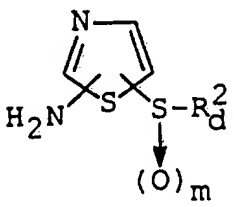
or its salt,

in which R^2_d, R^5_a and m are each as defined above, and

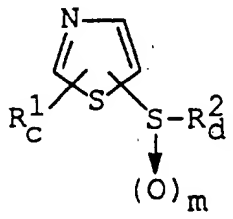
R^4_b is lower alkyl which may have suitable substituent(s),

or

(12) reacting a compound of the formula :



or its reactive derivative at the amino group or a salt thereof with alkali metal isocyanate to give a compound of the formula :



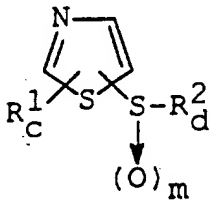
or its salt,

in which R_d^2 and m are each as defined above, and

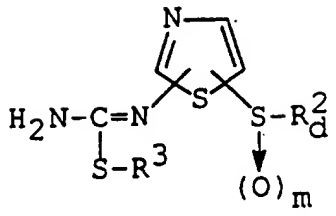
R_c^1 is thioureido,

or

(13) subjecting a compound of the formula :

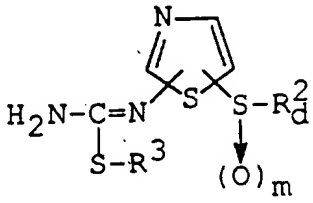


or its salt to alkylation to give a compound of the formula :

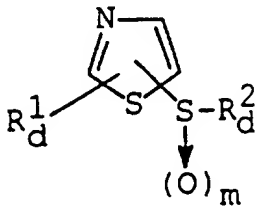


or its salt,
in which R^1_c, R^2_d, R^3 and m are each as defined above,
or

(14) reacting a compound of the formula :



or its salt with ammonia to give a compound of the formula :



or its salt,
in which R^2_d, R^3 and m are each as defined above, and
R^1_d is guanidino.

11. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

12. A use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a medicament.

13. A method for the prophylactic or therapeutic treatment of thrombocytopenia, rheumatism, nephritis, tumor or side effect of an antitumor agent which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

14. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.